REMARKS

This paper is filed in Response to the final Office Action mailed July 9, 2008. Claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 are pending, and have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. New claims 79 to 103, have been added. Accordingly, upon entry of this paper, claims 79 to 103 are under consideration.

Regarding the Interviews

Applicants thank the Examiner and their supervisor for the discussion on July 24, 2008, and the various subsequent discussions, during which time all rejections of record were discussed. During the last discussion, it was indicated that the new claims submitted herewith would be allowable.

Regarding the New Claims

New claims 79 to 103 are supported throughout the specification. In particular, claims 79 to 103 are supported, for example, by originally filed claims 1 to 16, at page 4, lines 1-13 at page 10, lines 4-20; at page 13, line 8, to page 14, line 8; and at page . More particular support for the term "epitope of the antigen expressed by...." one or more of the recited cell lines can be found, for example, at page 2, lines 6-7; and at page 17, lines 15-18, which discloses that the discovered class of polypeptides react with an epitope specific for cancer cells, and CM-1 monoclonal antibody, and other antibodies, or fragments thereof, that are specific for the antigen recognized by CM-1. Claim 94 is more particularly supported, for example, at page 22, lines 20-26, which discloses among other things that "variants include, for example, deletions from, or insertions or substitutions of, residues within the amino acid sequence of the CM-1 antibody. Any combination of deletion, insertion, and substitution can be made...." It is noted that in the second sentence, that each of the recited claim terms, namely "deletion" and "insertion" are singular. Claim 94 is also more particularly supported, for example, at page 23, lines 3-6, which discloses among other things that "[t]he sites for mutation can be modified individually or in series, e.g., (by 1) substituting first with...., or (2) deleting the target residue," which means that a single residue can be targeted for modification. Claim 103 is more particularly supported, for example, at page 17, lines 19-24, and by the ATCC deposit receipt immediately following

Figure 9 of the patent specification, which designates the cell line expressing the CM-1 antibody as having a Deposit of DSM ACC 2584. Thus, as claims 79 to 103 are supported by the originally filed specification, no new matter has been added and entry thereof is respectfully requested.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The rejection of claims 1, 2, 4, 7 to 9, 12 to 16 and 54 to 78 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. According to the Patent Office, allegedly the specification does not enable the skilled artisan to make and use the invention commensurate in scope with the claims.

Claims 1, 2, 4, 7 to 9, 12 to 16 and 54 to 78 have been cancelled herein without prejudice. The rejection will therefore be addressed insofar as if applied to claims 79 to 103.

The proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988).

Enablement of the claims here is analogous to *In re Wands*, in which the court held in 1988 that producing antibodies having binding activity did not require undue experimentation. In this regard, in view of the heavy and light chain variable region sequences disclosed in the specification, antibodies, fragments and variants thereof could be produced using routine methods disclosed in the specification or that were known in the art. In addition, the specification discloses assays for measuring binding, cell proliferation and apoptosis that do not require undue experimentation (page 44, Example 3, to page 49, Example 6). Thus, in view of the guidance in the specification and knowledge in the art regarding antibody structure and function at the time of the invention, and that antibody variants and functional fragments having the requisite activity could be produced using routine methods disclosed in the specification or that were known in the art at the time of the invention, one skilled in the art could make and use the claimed antibodies and functional fragments without undue experimentation.

As pointed out in the record, the level of knowledge with respect to antibody structure and function was high at the time of the invention. In particular, knowledge regarding antibody

structure and function, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of framework regions (FRs) was known. The role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding were also well understood by the skilled artisan at the time of the invention. Consequently, the level of knowledge concerning antibody structure and function at the time of the invention was high.

Because the level of knowledge in the art with respect to antibody structure and function was high at the time of the invention, the skilled artisan would know residues of SEQ ID NO:1 and SEQ ID NO:3 that would be amenable to substitution and would therefore be able to predict with reasonable certainty antibody variants of SEQ ID NO:1 and SEQ ID NO:3 that would have at least partial cell binding activity. For example, the skilled artisan could make a conservative amino acid substitution outside of a CDR or FR with reasonable certainty that the substituted sequence would retain at least partial activity of a non-substituted sequence. Given the large number of amino acids outside the CDR and FR regions, as well as the large number of amino acids outside of antibody variable regions, clearly many variants produced would have at least partial cell binding activity of non-variant SEQ ID NO:1 or SEQ ID NO:3. In addition, the skilled artisan would know that given the contribution of CDRs to antigen binding a large number of non-conservative amino acid substitutions in the CDRs of SEQ ID NO:1 or SEQ ID NO:3 would likely reduce or eliminate binding, and therefore not introduce a large number of non-conservative substitutions or delete a large number of amino acids of the CDRs of SEQ ID NO:1 or SEQ ID NO:3. Consequently, in view of the guidance in the specification and the high level of knowledge in the art regarding antibody structure and function, the skilled artisan would know of regions and particular residues that would be more or less amenable to substitution and could therefore predict variants and fragments that are likely to have at least partial function of non-variant sequence without actually producing variants and fragments.

In addition, the level of skill in the art regarding producing antibodies and functional fragments thereof was high. For example, conventional methods of producing antibody variants without undue experimentation are disclosed in the specification (page 22, line 16, to page 24, line 9; and page 21, line 16, to page 22, line 14). Such methods include conservative amino acid substitutions at pre-determined locations (page 23, line 23, to page 24, line 9). Furthermore, methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art

and were routine at the time of the invention (*e.g.*, using recombinant techniques). Thus, if the skilled artisan wished to produce antibody variants and functional fragments, in view of the guidance in the specification and knowledge in the art at the time of the invention, producing recombinant proteins would not require undue experimentation.

Furthermore, methods of identifying antibody fragments and variants having the recited binding or other activities without undue experimentation are also taught by the specification and were also known in the art at the time of the invention. In particular, methods for measuring antibody binding to the recited cell lines and ascertaining cell proliferation and apoptosis are disclosed in the specification (page 44, Example 3, to page 49, Example 6). Thus, in view of the guidance in the specification and the high level of skill in the art at the time of the invention, one skilled in the art could identify antibodies and fragments that bind to the epitope of the antigen to which the CM-1 antibody produced by a cell line deposited as DSM ACC 2584 specifically binds, without undue experimentation.

Moreover, enablement under 35 U.S.C. §112, first paragraph does not require that every amino acid of a given protein, such as an antibody, be analyzed so that the skilled artisan knows or is able to predict with absolute certainty the effect of each and every substitution, insertion or deletion *a priori*. Rather, in view of the guidance in the specification and knowledge in the art at the time of the invention, the skilled artisan could produce and identify antibody variants and fragments of SEQ ID NO:1 and SEQ ID without knowing in advance the effect of particular substitutions or deletions on activity without undue experimentation.

In addition to the foregoing, the previously filed Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers corroborates Applicants' position that the claims are adequately enabled under 35 U.S.C. §112, first paragraph. For the sake of brevity, Applicants will refrain from reiterating the content of this Declaration, but respectfully request consideration of the executed Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers.

In view of the foregoing and the reasons of record, one skilled in the art could readily produce antibodies and functional fragments of claims 79 to 103 without undue experimentation. Accordingly, claims 79 to 103 are adequately enabled and Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

II. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The rejection of claims 76 to 78 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. According to the Patent Office, allegedly the claims lack support in the as-field specification.

Claims 76 to 78 have been cancelled herein without prejudice. The rejection will therefore be addressed insofar as if applied to claim 94.

The written description requirement under 35 U.S.C. §112, first paragraph is "to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, F.2d 588, 592 (CCPA 1977). A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Notably, the courts have never required that the subject matter of the claims be described literally or using the same terms- there is no "*in haec verba*" requirement

As discussed above, claim 94 is particularly supported, for example, at page 22, lines 20-26, which discloses among other things that "variants include, for example, deletions from, or insertions or substitutions of, residues within the amino acid sequence of the CM-1 antibody. Any combination of deletion, insertion, and substitution can be made...." Notably, in the second sentence of the foregoing passage in the specification, each of the terms, "deletion" and "insertion" which appear in claim 94 are singular. In addition, claim 94 is more particularly supported, for example, at page 23, lines 3-6, which discloses among other things that "[t]he sites for mutation can be modified individually or in series, e.g., by (1) substituting first with...., or (2) deleting the target residue," which means that a single residue can be targeted for modification.

In view of the foregoing one skilled in the art would have clearly recognized that a deletion or insertion, or substitution can be one amino acid. Consequently, Applicants

respectfully state that claim 94 is adequately described to one skilled in the art and therefore satisfies the written description requirement under 35 U.S.C. §112, first paragraph.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 79 to 103 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

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